PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 38147-0026WO	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/US05/03857	International filing date *(day/month/year)* 07 February 2005 (07.02.2005)	Priority date *(day/month/year)* 05 February 2004 (05.02.2004)

International Patent Classification (IPC) or national classification and IPC

IPC: **C07H 21/04**(2006.01);**A61K 48/00**(2006.01)
USPC: 536/24.5;514/44

Applicant

INTRADIGM CORPORATION

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 3 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 12 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) _____ , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06 September 2005 (06.09.2005)	25 May 2006 (25.05.2006)
Name and mailing address of the IPEA/ US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Authorized officer Kimberly Chong Telephone No. 571-272-0564

Form PCT/IPEA/409 (cover sheet)(April 2005)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US05/03857

Box No. I Basis of the report

1. With regard to the **language**, this report is based on:
   - ☒ the international application in the language in which it was filed.
   - ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of:
     - ☐ international search (under Rules 12.3 and 23.1(b))
     - ☐ publication of the international application (under Rule 12.4(a))
     - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:
   - ☐ the international application as originally filed/furnished
   - ☒ the description:
     pages 1-62 as originally filed/furnished
     pages* NONE received by this Authority on _____
     pages* NONE received by this Authority on _____
   - ☒ the claims:
     pages 63-66 as originally filed/furnished
     pages* NONE as amended (together with any statement) under Article 19
     pages* NONE received by this Authority on _____
     pages* NONE received by this Authority on _____
   - ☒ the drawings:
     pages NONE as originally filed/furnished
     pages* 1/12-12/12 received by this Authority on 06 September 2005 (06.09.2005)
     pages* NONE received by this Authority on _____
   - ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages _____
   - ☐ the claims, Nos. _____
   - ☐ the drawings, sheets/figs _____
   - ☐ the sequence listing (*specify*): _____
   - ☐ any table(s) related to the sequence listing (*specify*): _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages _____
   - ☐ the claims, Nos. _____
   - ☐ the drawings, sheets/figs _____
   - ☐ the sequence listing (*specify*): _____
   - ☐ any table(s) related to the sequence listing (*specify*): _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US05/03857

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 5-13, 15-16, 30-45, 47	YES
	Claims 1-4, 14, 17-29, 46	NO
Inventive Step (IS)	Claims NONE	YES
	Claims 1-47	NO
Industrial Applicability (IA)	Claims 1-47	YES
	Claims NONE	NO

2. Citations and Explanations (Rule 70.7)

Claims 1-4, 14, 17-29 and 46 lack novelty under PCT Article 33(2) as being anticipated by Reich et al. Reich et al. teach a composition comprising a dsRNA in a pharmaceutical carrier (see page 211 column 1). Reich et al. further teach the composition comprising a dsRNA targeted to VEGF, a gene associated with neovascularization (see page 211, column 2). Reich et al. further teach a method of treating ocular disease in a subject comprising administering a dsRNA that inhibits expression of a gene that promotes neovascularization (see page 211 column 2).

Claims 5-13, 15-16, 30-45, 47 lack an inventive step under PCT Article 33(3) as being obvious over Velesky et al. in view of Hammond et al. and in further view of Li et al. Valesky teach a composition comprising antisense molecules targeted to FGF and FGF-R (see page 104-105). Valesky et al. further teach a method of treating angiogenesis by injecting the compositions comprising two genes targeted to angiogenesis (see page 105). Valesky does not teach using dsRNA nor does Valesky teach using a composition comprising at least two dsRNA . Hammond et al. teach two methods for silencing specific genes: antisense and RNA interference. Hammond et al. teach that although antisense methods are straightforward techniques for probing gene function, the methods have suffered from "... questionable specificity and incomplete efficacy." (see page 110, column 1). Hammond et al. further teach ..."dsRNAs have been shown to inhibit gene expression in a sequence-specific manner". Li et al. teach targeted silencing of multiple genes using dsRNA (see paragraph 105) in cells, including human (see paragraph 033).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make dsRNAs targeted to multiple genes associated with neovascularization.

One would have been motivated to use dsRNAs targeted to a multiple genes instead of an antisense because Hammond et al. teach using dsRNA to inhibit gene expression is more sequence specific than using antisense methodologies and RNAi using dsRNA is a more potent method requiring only a few molecules of dsRNA per cell and Li et al. teach using dsRNA to target multiple genes. One would have been motivated to target multiple genes because concurrent inhibition is advantageous to treat a disease associated with multiple genes, such as neovascularization.

Finally, one would have a reasonable expectation of success because Valesky et al. teach inhibition using antisense molecules targeted FGF and FGF-R genes, Hammond et al. teach that of the two methods used for silencing gene function, RNAi using dsRNA is more potent and sequence specific than antisense and finally Li et al. teach making silencing of multiple genes using dsRNA targeted to multiple genes.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.